

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-75 (Canceled)

76. (Currently amended) A composition, comprising:

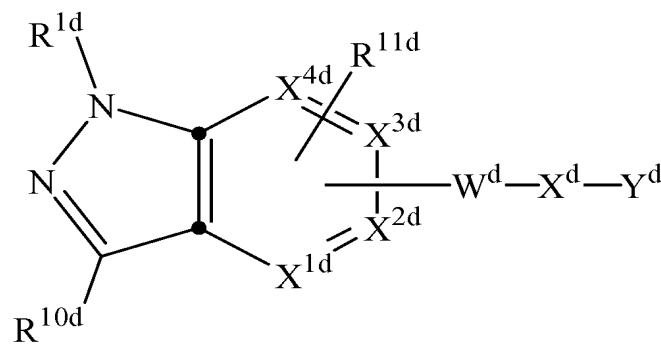
a metal;

chelator capable of chelating the metal ;

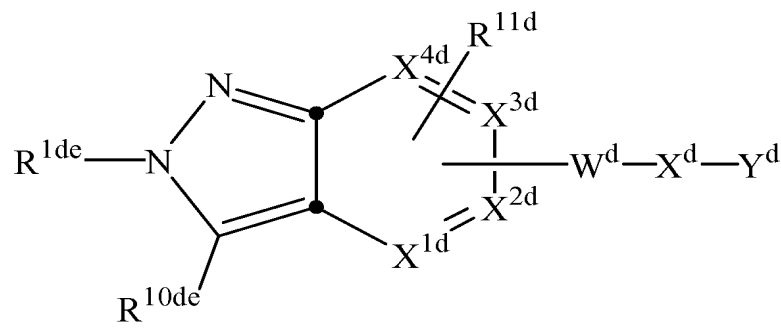
an indazole nonpeptide targeting moiety covalently bound to the chelator, either directly or via an optional interposed linking group, wherein the targeting moiety binds to a receptor that is upregulated during angiogenesis; and

at least one of a chemotherapeutic agent or a radiosensitizer agent;

wherein the indazole nonpeptide targeting moiety is represented by (Q)_d wherein Q is independently a compound of Formulae (Ia) or (Ib):



(Ia)



DOCKET NO.: BMS-0690 (DM-6999-A)
Application No.: 09/599,890
Office Action Dated: May 2, 2006

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37 CFR § 1.116

(Ib)

wherein:

X^{1d} is CH, C- W^d- X^d- Y^d, or C bonded to the linking group;

X^{2d} is CH or C- W^d- X^d- Y^d;

X^{3d} is CR^{11d} or C- W^d- X^d- Y^d;

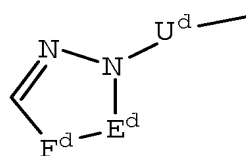
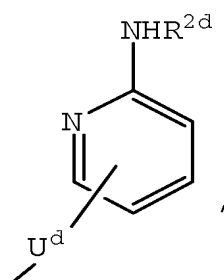
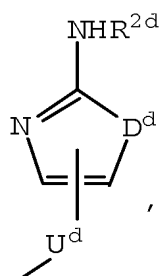
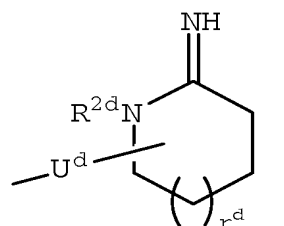
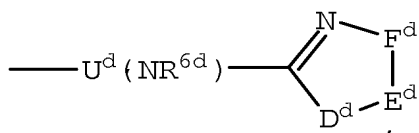
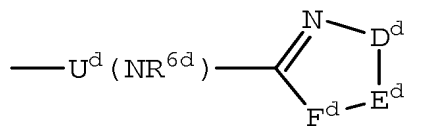
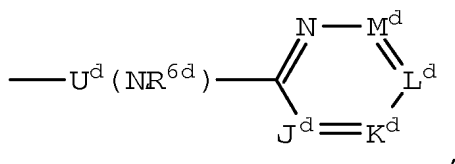
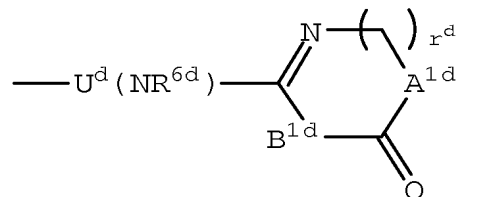
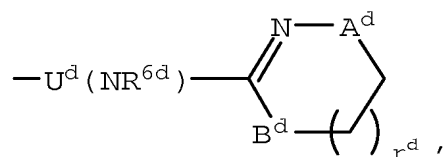
X^{4d} is CR^{11d};

R^{1d} is R^{1de}, C₁-C₆ alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₃-C₆ alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₃-C₇ cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₄-C₁₁ cycloalkylalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}, or aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d};

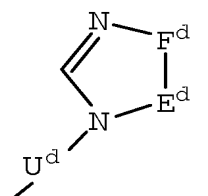
R^{1de} is:

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or



A^d and B^d are independently $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{R}^{2d})-$, or $-\text{C}(=\text{O})-$;

A^{1d} and B^{1d} are independently -CH₂- or -N(R^{3d})-;

D^d is -N(R^{2d})-, -O-, -S-, -C(=O)- or -SO₂-;

E^d, F^d is -C(R^{4d})=C(R^{5d})-, -N=C(R^{4d})-, -C(R^{4d})=N-, or -C(R^{4d})₂C(R^{5d})₂-;

J^d, K^d, L^d and M^d are independently:

-C(R^{4d})-, -C(R^{5d})- or -N-, provided that at least one of J^d, K^d, L^d and M^d is not -N-;

provided that when R^{1d} is R^{1de} then one of X^{1d} and X^{2d} is C- W^d- X^d- Y^d, and
when R^{10d} is R^{1de} then X^{3d} is C- W^d- X^d- Y^d;

R^{2d} is H, C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonyl, (C₁-C₆ alkoxy)carbonyl; (C₁-C₆ alkyl)aminocarbonyl, C₃-C₆ alkenyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, heteroaryl(C₁-C₆ alkyl)carbonyl, heteroarylcarbonyl, aryl(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)carbonyl-, arylcarbonyl, C₁-C₆ alkylsulfonyl, arylsulfonyl, aryl(C₁-C₆ alkyl)sulfonyl, heteroarylsulfonyl, heteroaryl(C₁-C₆ alkyl)sulfonyl, aryloxy carbonyl, or aryl(C₁-C₆ alkoxy)carbonyl, wherein said aryl groups are substituted with 0-2 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and nitro;

R^{3d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, or heteroaryl(C₁-C₆ alkyl)-;

R^{4d} and R^{5d} are independently H, C₁-C₄ alkoxy, NR^{2d}R^{3d}, halogen, NO₂, CN, CF₃, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)carbonyl, (C₁-C₆ alkoxy)carbonyl, or arylcarbonyl, or

alternatively, when substituents on adjacent atoms, R^{4d} and R^{5d} can be taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or 5-7 membered heterocyclic aromatic or non-aromatic ring system, said carbocyclic or heterocyclic ring being optionally substituted with 0-2 groups selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, cyano, amino, CF₃, and NO₂;

U^d is:

____-(CH₂)_n^d-,

-(CH₂)_n^d(CR^{7d}=CR^{8d})(CH₂)_m^d-,

$-(CH_2)_n^d(C\equiv C)(CH_2)_m^d-$,
 $-(CH_2)_n^dQ^d(CH_2)_m^d-$,
 $-(CH_2)_n^dO(CH_2)_m^d-$,
 $-(CH_2)_n^dN(R^{6d})(CH_2)_m^d-$,
 $-(CH_2)_n^dC(=O)(CH_2)_m^d-$,
 $-(CH_2)_n^d(C=O)N(R^{6d})(CH_2)_m^d-$,
 $-(CH_2)_n^dN(R^{6d})(C=O)(CH_2)_m^d-$, or
 $-(CH_2)_n^dS(O)_p^d(CH_2)_m^d-$;

wherein one or more of the methylene groups in U^d is optionally substituted with R^{7d} .

Q^d is 1,2-cycloalkylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 2,4-pyridinylene, or 3,4-pyridazinylene;

R^{6d} is H, C_1 - C_4 alkyl, or benzyl;

R^{7d} and R^{8d} are independently H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_4 - C_{11} cycloalkylalkyl, aryl, aryl(C_1 - C_6 alkyl)-, or heteroaryl(C_0 - C_6 alkyl)-;

R^{10d} is H, R^{1de} , C_1 - C_4 alkoxy substituted with 0-1 R^{21d} , $N(R^{6d})_2$, halogen, NO_2 , CN, CF_3 , CO_2R^{17d} , $C(=O)R^{17d}$, $CONR^{17d}R^{20d}$, $-SO_2R^{17d}$, $-SO_2NR^{17d}R^{20d}$, C_1 - C_6 alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_6 alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_7 cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_4 - C_{11} cycloalkylalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d} , or aryl(C_1 - C_6 alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d} ;

R^{10de} is H, C_1 - C_4 alkoxy substituted with 0-1 R^{21d} , $N(R^{6d})_2$, halogen, NO_2 , CN, CF_3 , CO_2R^{17d} , $C(=O)R^{17d}$, $CONR^{17d}R^{20d}$, $-SO_2R^{17d}$, $-SO_2NR^{17d}R^{20d}$, C_1 - C_6 alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_6 alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_7 cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_4 - C_{11} cycloalkylalkyl

substituted with 0-1 R^{15d} or 0-1 R^{21d}, aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}, or aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}.

R^{11d} is H, halogen, CF₃, CN, NO₂, hydroxy, NR^{2d}R^{3d}, C₁-C₄ alkyl substituted with 0-1 R^{21d}, C₁-C₄ alkoxy substituted with 0-1 R^{21d}, aryl substituted with 0-1 R^{21d}, aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{21d}, (C₁-C₄ alkoxy)carbonyl substituted with 0-1 R^{21d}, (C₁-C₄ alkyl)carbonyl substituted with 0-1 R^{21d}, C₁-C₄ alkylsulfonyl substituted with 0-1 R^{21d}, or C₁-C₄ alkylaminosulfonyl substituted with 0-1 R^{21d}.

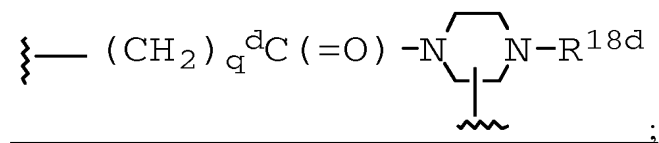
W^d is:

-(C(R^{12d})₂)_q^dC(=O)N(R^{13d})-, or

-C(=O)-N(R^{13d})-(C(R^{12d})₂)_q^d;

X^d is -C(R^{12d})(R^{14d})-C(R^{12d})(R^{15d})-; or

alternatively, W^d and X^d can be taken together to be



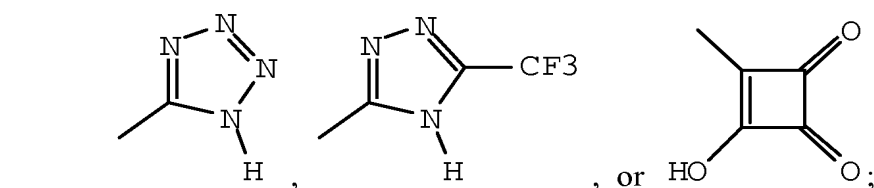
R^{12d} is H, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, (C₁-C₄ alkyl)carbonyl, aryl, or aryl(C₁-C₆ alkyl)-;

R^{13d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkylmethyl, or aryl(C₁-C₆ alkyl)-;

R^{14d} is H, C₁-C₆ alkylthio(C₁-C₆ alkyl)-, aryl(C₁-C₁₀ alkylthioalkyl)-, aryl(C₁-C₁₀ alkoxyalkyl)-, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxyalkyl, C₁-C₆ hydroxyalkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, heteroaryl(C₁-C₆ alkyl)-, aryl, heteroaryl, CO₂R^{17d}, C(=O)R^{17d}, or CONR^{17d}R^{20d}, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-1 R^{16d} or 0-2 R^{11d}.

R^{15d} is H, R^{16d}, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxyalkyl, C₁-C₁₀ alkylaminoalkyl, di(C₁-C₁₀ alkyl)aminoalkyl, (C₁-C₁₀ alkyl)carbonyl, aryl(C₁-C₆ alkyl)carbonyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, heteroaryl(C₁-C₆ alkyl)-, aryl, heteroaryl, CO₂R^{17d}, C(=O)R^{17d}, CONR^{17d}R^{20d}, SO₂R^{17d}, or SO₂NR^{17d}R^{20d}, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-2 R^{11d}.

Y^d is -COR^{19d}, -SO₃H, -PO₃H, tetrazolyl, -CONHNHSO₂CF₃, -CONHSO₂R^{17d}, -CONHSO₂NHR^{17d}, -NHCOCF₃, -NHCONHSO₂R^{17d}, -NHSO₂R^{17d}, -OPO₃H₂, -OSO₃H, -PO₃H₂, -SO₃H, -SO₂NHCOR^{17d}, -SO₂NHCO₂R^{17d},



R^{16d} is:

-N(R^{20d})-C(=O)-O-R^{17d},
-N(R^{20d})-C(=O)-R^{17d},
-N(R^{20d})-C(=O)-NH-R^{17d},
-N(R^{20d})SO₂-R^{17d}, or
-N(R^{20d})SO₂-NR^{20d}R^{17d}.

R^{17d} is C₁-C₁₀ alkyl optionally substituted with a bond to the linking group, C₃-C₁₁ cycloalkyl optionally substituted with a bond to the linking group, aryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking group, (C₁-C₆ alkyl)aryl optionally substituted with a bond to the linking group, heteroaryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking group, (C₁-C₆ alkyl)heteroaryl optionally substituted with a bond to the linking group, biaryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking group, heteroaryl optionally substituted with a bond to the linking group, aryl optionally

substituted with a bond to the linking group, biaryl optionally substituted with a bond to the linking group, or a bond to the linking group, wherein said aryl, biaryl or heteroaryl groups are also optionally substituted with 0-3 substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, aryl, heteroaryl, halo, cyano, amino, CF₃, or NO₂;

R^{18d} is:

_____ -H,

_____ -C(=O)-O-R^{17d},

_____ -C(=O)-R^{17d},

_____ -C(=O)-NH-R^{17d},

_____ -SO₂-R^{17d}, or

_____ -SO₂-NR^{20d}R^{17d}.

R^{19d} is hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy, aryloxy, aryl(C₁-C₆ alkoxy)-, C₃-C₁₀ alkylcarbonyloxyalkyloxy, C₃-C₁₀ alkoxy carbonyloxyalkyloxy, C₂-C₁₀ alkoxy carbonylalkyloxy, C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonylalkyloxy, C₇-C₁₁ aryloxy carbonylalkyloxy, C₈-C₁₂ aryloxy carbonyloxyalkyloxy, C₈-C₁₂ arylcarbonyloxyalkyloxy, C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy, C₅-C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀-C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or

(R^{11d})(R^{12d})N-(C₁-C₁₀ alkoxy)-;

R^{20d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, or heteroaryl(C₁-C₆ alkyl)-;

R^{21d} is COOH or NR^{6d}₂;

m^d is 0-4;

n^d is 0-4;

t^d is 0-4;

p^d is 0-2;

q^d is 0-2;

r^d is 0-2; and

d is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

with the following provisos:

(1) t^d , n^d , m^d and q^d are chosen such that the number of atoms connecting R^{1d} and Y^d is in the range of 10-14; and

(2) n^d and m^d are chosen such that the value of n^d plus m^d is greater than one unless U^d is



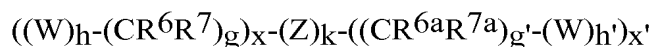
77. (Previously Presented) The composition of claim 76, wherein the metal, targeting moiety, chelator, and optional linking group are a diagnostic or therapeutic metallopharmaceutical.

78. (Previously Presented) The composition of claim 76, wherein the chemotherapeutic agent is mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitio stanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftotox, interleukin-2, or leutinizing hormone releasing factor.

79. (Previously Presented) The composition of claim 76, wherein the radiosensitizer agent is 2-(3-nitro-1,2,4-triazol-1-yl)-N-(2-methoxyethyl)acetamide, N-(3-nitro-4-quinolinyl)-4-morpholinecarboxamide, 3-amino-1,2,4-benzotriazine-1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1-acetamide, 1-(2-nitroimidazol-1-yl)-3-(1-piperidinyl)-2-propanol, or 1-(2-nitro-1-imidazolyl)-3-(1-aziridino)-2-propanol.

80. (Previously Presented) The composition of claim 76, wherein the linking group is present between the targeting moiety and the chelator.

81. (Currently amended) The composition of claim 76, wherein the linking group has a formula:



wherein:

W is independently selected at each occurrence from ~~the group~~: O, S, NH, NHC(=O), C(=O)NH, NR⁸C(=O), C(=O)NR⁸, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, SO₂NH, ~~(OCH₂CH₂)₂₀₋₂₀₀ (OCH₂CH₂)₀₋₁₀, (CH₂CH₂O)₂₀₋₂₀₀ (CH₂CH₂O)₀₋₁₀, (OCH₂CH₂CH₂)₂₀₋₂₀₀ (OCH₂CH₂CH₂)₀₋₁₀, (CH₂CH₂CH₂O)₂₀₋₂₀₀ (CH₂CH₂CH₂O)₀₋₁₀, and or (aa)_t~~;

aa is independently at each occurrence an amino acid;

Z is selected from ~~the group~~: aryl substituted with 0-3 R¹⁰, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁰, ~~and or~~ a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and or~~ O and substituted with 0-3 R¹⁰;

R⁶, R^{6a}, R⁷, R^{7a}, and R⁸ are independently selected at each occurrence from ~~the group~~: H, =O, COOH, SO₃H, PO₃H, C₁₋₅ alkyl substituted with 0-3 R¹⁰, aryl substituted with 0-3 R¹⁰, benzyl substituted with 0-3 R¹⁰, ~~and~~ C₁₋₅ alkoxy substituted with 0-3 R¹⁰,

NHC(=O)R^{11} , C(=O)NHR^{11} , NHC(=O)NHR^{11} , NHR^{11} , R^{11} , ~~and~~ or a bond to the chelator;

R^{10} is independently selected at each occurrence from ~~the group:~~ a bond to the chelator, COOR^{11} , C(=O)NHR^{11} , NHC(=O)R^{11} , OH , NHR^{11} , SO_3H , PO_3H , $-\text{OPO}_3\text{H}_2$, $-\text{OSO}_3\text{H}$, aryl substituted with 0-3 R^{11} , C_{1-5} alkyl substituted with 0-1 R^{12} , C_{1-5} alkoxy substituted with 0-1 R^{12} , ~~and~~ or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and~~ or O and substituted with 0-3 R^{11} ;

R^{11} is independently selected at each occurrence from ~~the group:~~ H, alkyl substituted with 0-1 R^{12} , aryl substituted with 0-1 R^{12} , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and~~ or O and substituted with 0-1 R^{12} , C_{3-10} cycloalkyl substituted with 0-1 R^{12} , polyalkylene glycol substituted with 0-1 R^{12} , carbohydrate substituted with 0-1 R^{12} , cyclodextrin substituted with 0-1 R^{12} , amino acid substituted with 0-1 R^{12} , polycarboxyalkyl substituted with 0-1 R^{12} , polyazaalkyl substituted with 0-1 R^{12} , peptide substituted with 0-1 R^{12} , wherein the peptide is comprised of 2-10 amino acids, 3,6-O-disulfo-B-D-galactopyranosyl, bis(phosphonomethyl)glycine, ~~and~~ or a bond to the chelator;

R^{12} is a bond to the chelator;

k is selected from 0, 1, ~~and~~ or 2;

h is selected from 0, 1, ~~and~~ or 2;

h' is selected from 0, 1, ~~and~~ or 2;

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

x is selected from 0, 1, 2, 3, 4, ~~and~~ or 5; and

x' is selected from 0, 1, 2, 3, 4, ~~and~~ or 5.

82. (Previously Presented) The composition of claim 76, wherein the receptor is $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

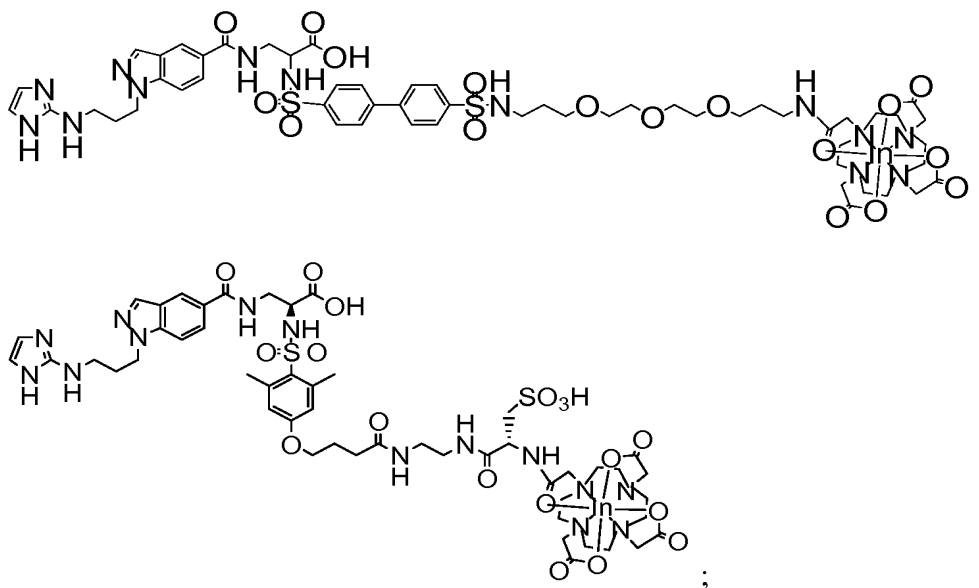
83. (Previously Presented) The composition of claim 76, wherein the metal is ^{99m}Tc , ^{95}Tc , ^{111}In , ^{62}Cu , ^{64}Cu , ^{67}Ga , or ^{68}Ga .
84. (Previously Presented) The composition of claim 76, wherein the metal is ^{99m}Tc or ^{95}Tc .
85. (Previously Presented) The composition of claim 76, wherein the metal is ^{99m}Tc .
86. (Previously Presented) The composition of claim 76, wherein the metal is ^{111}In .
87. (Previously Presented) The composition of claim 76, further comprising a first ancillary ligand and a second ancillary ligand.
88. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:
- ^{99m}Tc (((4-(4-(((3-(2-(2-(3-((6-(diazenido)(3-pyridyl))carbonylamino)propoxy)ethoxy)ethoxy)propyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)propanoic acid) (tricine)(TPPTS);
- ^{99m}Tc (2-(2-((5-(N-(1,3-bis(3-(2-(2-(3-(((4-(4-(((1-carboxy-2-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)ethyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)propyl)carbamoyl)(2-pyridyl))2-diazenido) (tricine)(TPPTS);
- ^{99m}Tc (2-((6-(diazenido)(3-pyridyl))carbonylamino)-4-(N-(3-(2-(2-(3-(((4-(4-(((1-carboxy-2-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)ethyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)butanoic acid) (tricine)(TPPTS);
- ^{99m}Tc (2-(6-((6-(diazenido)(3-pyridyl))carbonylamino)hexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)-propanoic acid) (tricine)(TPPTS);

^{99m}Tc (2-((6-(diazenido)(3-pyridyl))carbonylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)propanoic acid (tricine)(TPPTS);

^{99m}Tc [2-[[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid)(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid)) (tricine)(TPPTS); or

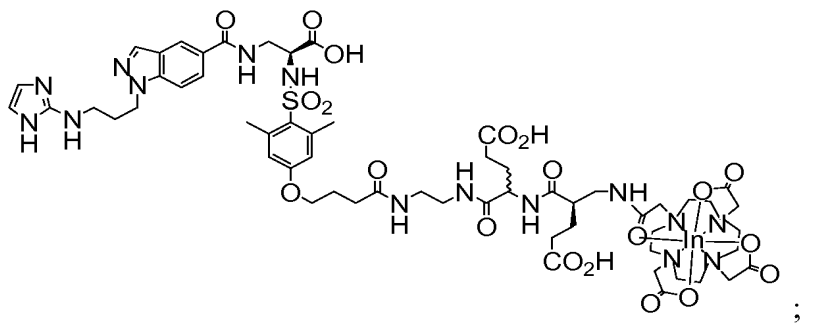
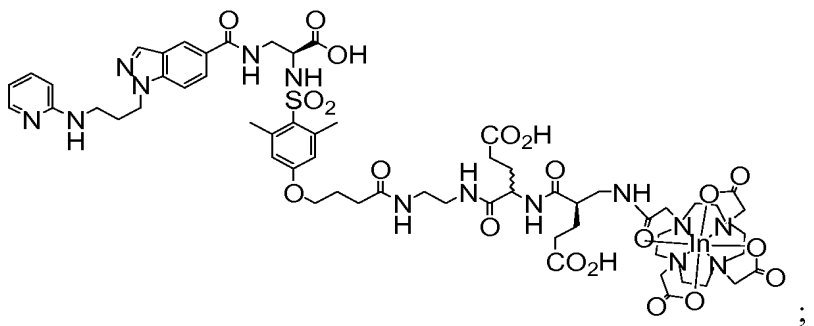
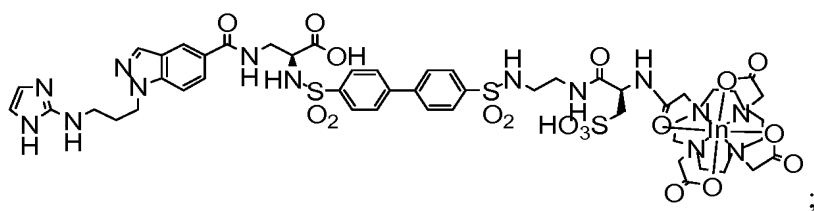
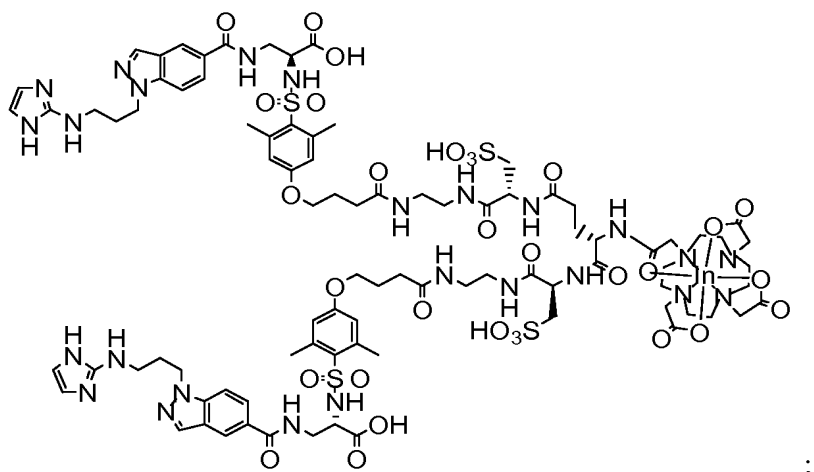
^{99m}Tc ([2-[[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu-bis-[Glu(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid)(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid))] (tricine)(TPPTS).

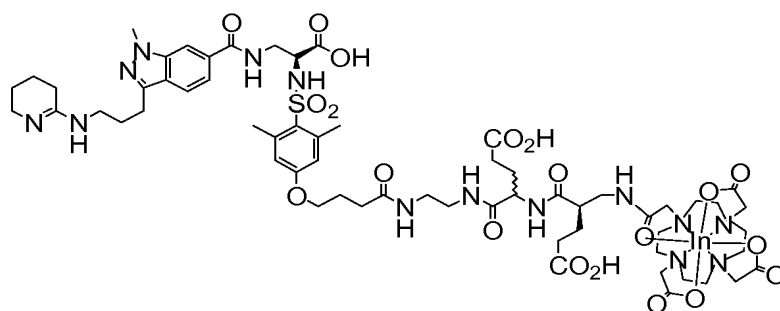
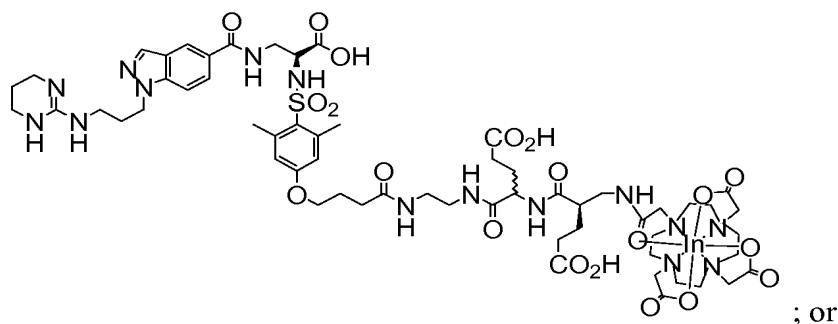
89. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:



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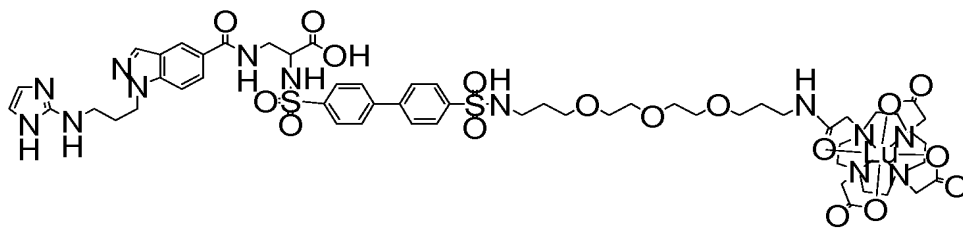
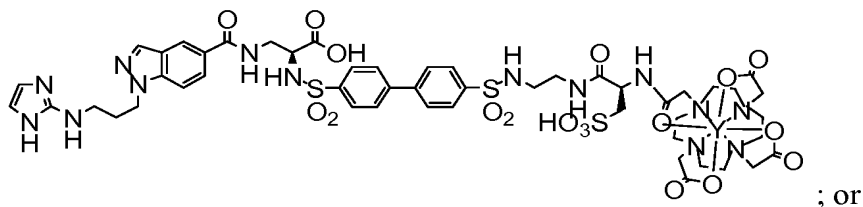
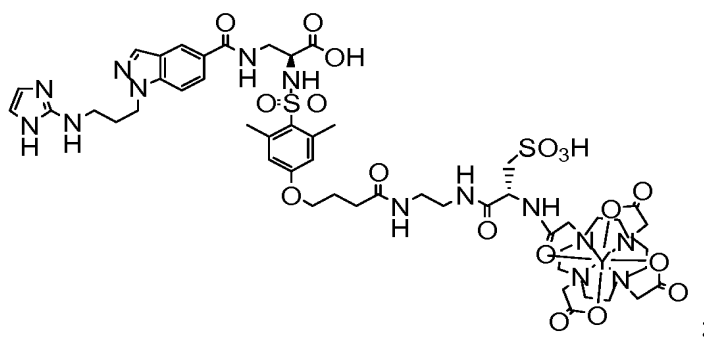
90. (Previously Presented) The composition of claim 76, wherein the metal is ^{33}P , ^{125}I , ^{186}Re , ^{188}Re , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{149}Pm , ^{90}Y , ^{212}Bi , ^{103}Pd , ^{109}Pd , ^{159}Gd , ^{140}La , ^{198}Au , ^{199}Au , ^{169}Yb , ^{175}Yb , ^{165}Dy , ^{166}Dy , ^{67}Cu , ^{105}Rh , ^{111}Ag , or ^{192}Ir .

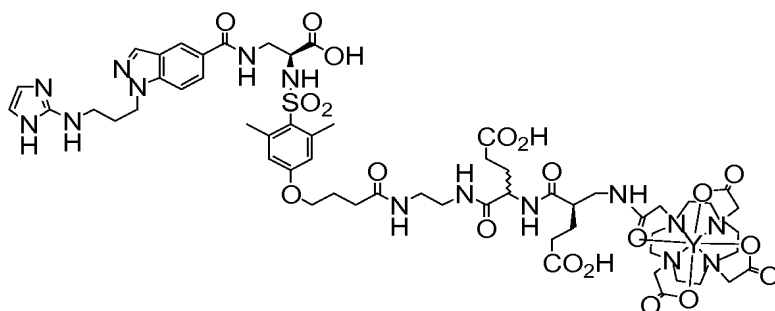
91. (Previously Presented) The composition of claim 76, wherein the metal is ^{153}Sm .

92. (Previously Presented) The composition of claim 76, wherein the metal is ^{177}Lu .

93. (Previously Presented) The composition of claim 76, wherein the metal is ^{90}Y .

94. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:

O=C(O)CNC(=O)c1ccc2nc3cnc(CCN3c4ccc5c2cnc5n4)c6ccc(cc6)S(=O)(=O)c7ccc(cc7)S(=O)(=O)NCCCOCCOCCOCCOCCN8C9C10C11C12C13C14C15C16C17C18C19C20C21C22C23C24C25C26C27C28C29C30C31C32C33C34C35C36C37C38C39C40C41C42C43C44C45C46C47C48C49C50C51C52C53C54C55C56C57C58C59C60C61C62C63C64C65C66C67C68C69C70C71C72C73C74C75C76C77C78C79C80C81C82C83C84C85C86C87C88C89C90C91C92C93C94C95C96C97C98C99C100C101C102C103C104C105C106C107C108C109C110C111C112C113C114C115C116C117C118C119C120C121C122C123C124C125C126C127C128C129C130C131C132C133C134C135C136C137C138C139C140C141C142C143C144C145C146C147C148C149C150C151C152C153C154C155C156C157C158C159C160C161C162C163C164C165C166C167C168C169C170C171C172C173C174C175C176C177C178C179C180C181C182C183C184C185C186C187C188C189C190C191C192C193C194C195C196C197C198C199C200C201C202C203C204C205C206C207C208C209C210C211C212C213C214C215C216C217C218C219C220C221C222C223C224C225C226C227C228C229C230C231C232C233C234C235C236C237C238C239C240C241C242C243C244C245C246C247C248C249C250C251C252C253C254C255C256C257C258C259C260C261C262C263C264C265C266C267C268C269C270C271C272C273C274C275C276C277C278C279C280C281C282C283C284C285C286C287C288C289C290C291C292C293C294C295C296C297C298C299C300C301C302C303C304C305C306C307C308C309C310C311C312C313C314C315C316C317C318C319C320C321C322C323C324C325C326C327C328C329C330C331C332C333C334C335C336C337C338C339C340C341C342C343C344C345C346C347C348C349C350C351C352C353C354C355C356C357C358C359C360C361C362C363C364C365C366C367C368C369C370C371C372C373C374C375C376C377C378C379C380C381C382C383C384C385C386C387C388C389C390C391C392C393C394C395C396C397C398C399C400C401C402C403C404C405C406C407C408C409C410C411C412C413C414C415C416C417C418C419C420C421C422C423C424C425C426C427C428C429C430C431C432C433C434C435C436C437C438C439C440C441C442C443C444C445C446C447C448C449C450C451C452C453C454C455C456C457C458C459C460C461C462C463C464C465C466C467C468C469C470C471C472C473C474C475C476C477C478C479C480C481C482C483C484C485C486C487C488C489C490C491C492C493C494C495C496C497C498C499C500C501C502C503C504C505C506C507C508C509C510C511C512C513C514C515C516C517C518C519C520C521C522C523C524C525C526C527C528C529C530C531C532C533C534C535C536C537C538C539C540C541C542C543C544C545C546C547C548C549C550C551C552C553C554C555C556C557C558C559C560C561C562C563C564C565C566C567C568C569C570C571C572C573C574C575C576C577C578C579C580C581C582C583C584C585C586C587C588C589C590C591C592C593C594C595C596C597C598C599C600C601C602C603C604C605C606C607C608C609C610C611C612C613C614C615C616C617C618C619C620C621C622C623C624C625C626C627C628C629C630C631C632C633C634C635C636C637C638C639C640C641C642C643C644C645C646C647C648C649C650C651C652C653C654C655C656C657C658C659C660C661C662C663C664C665C666C667C668C669C670C671C672C673C674C675C676C677C678C679C680C681C682C683C684C685C686C687C688C689C690C691C692C693C694C695C696C697C698C699C700C701C702C703C704C705C706C707C708C709C710C711C712C713C714C715C716C717C718C719C720C721C722C723C724C725C726C727C728C729C730C731C732C733C734C735C736C737C738C739C740C741C742C743C744C745C746C747C748C749C750C751C752C753C754C755C756C757C758C759C760C761C762C763C764C765C766C767C768C769C770C771C772C773C774C775C776C777C778C779C780C781C782C783C784C785C786C787C788C789C790C791C792C793C794C795C796C797C798C799C800C801C802C803C804C805C806C807C808C809C810C811C812C813C814C815C816C817C818C819C820C821C822C823C824C825C826C827C828C829C830C831C832C833C834C835C836C837C838C839C840C841C842C843C844C845C846C847C848C849C850C851C852C853C854C855C856C857C858C859C860C861C862C863C864C865C866C867C868C869C870C871C872C873C874C875C876C877C878C879C880C881C882C883C884C885C886C887C888C889C890C891C892C893C894C895C896C897C898C899C900C901C902C903C904C905C906C907C908C909C910C911C912C913C914C915C916C917C918C919C920C921C922C923C924C925C926C927C928C929C930C931C932C933C934C935C936C937C938C939C940C941C942C943C944C945C946C947C948C949C950C951C952C953C954C955C956C957C958C959C960C961C962C963C964C965C966C967C968C969C970C971C972C973C974C975C976C977C978C979C980C981C982C983C984C985C986C987C988C989C990C991C992C993C994C995C996C997C998C999

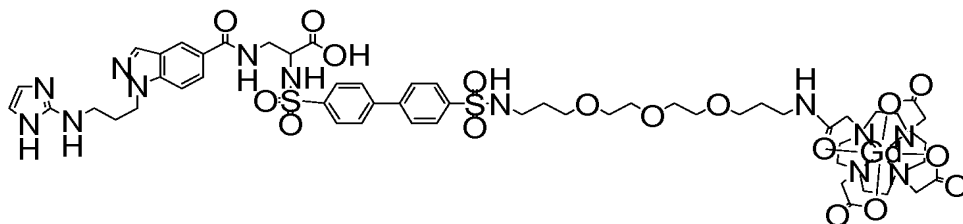


96. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is a MRI contrast agent, the metal is a paramagnetic metal ion selected from the group: Gd(III), Dy(III), Fe(III), and Mn(II), and the linking group is present between the targeting moiety and chelator.

97. (Previously Presented) The composition of claim 96, wherein the receptor is $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

98. (Previously Presented) The composition of claim 96, wherein the metal ion is Gd(III).

99. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:

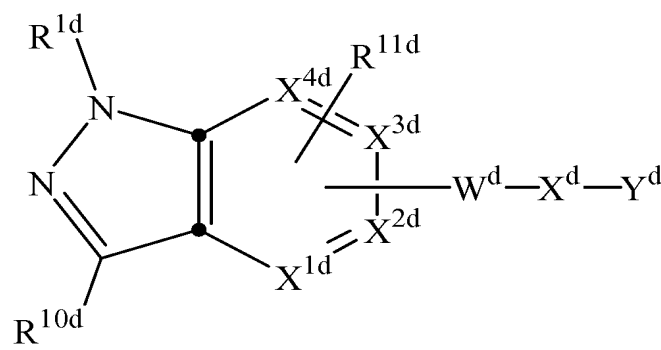


100. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is a X-ray contrast agent, the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir, the receptor is $\alpha_v\beta_3$ or $\alpha_v\beta_5$, and the linking group is present between the targeting moiety and chelator.

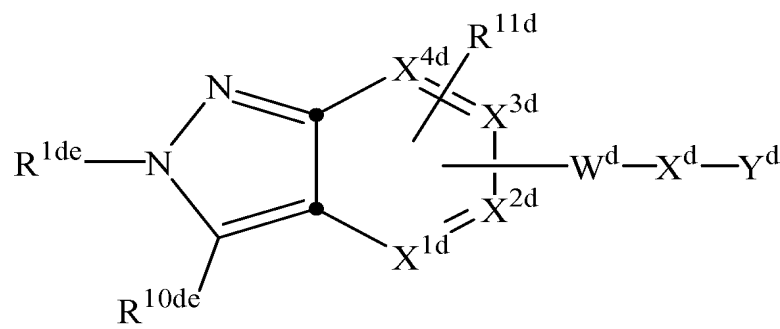
101. (Currently amended) A composition, comprising:

an indazole nonpeptide targeting moiety attached to a surfactant via a linking group,
wherein the targeting moiety binds to a receptor that is upregulated during angiogenesis; and
an echogenic gas.

wherein the indazole nonpeptide targeting moiety is represented by (Q)_d wherein Q is independently a compound of Formulae (Ia) or (Ib):



(Ia)



(Ib)

wherein:

X^{1d} is CH, C- W^d- X^d- Y^d, or C bonded to the linking group;

X^{2d} is CH or C- W^d- X^d- Y^d;

X^{3d} is CR^{11d} or C- W^d- X^d- Y^d;

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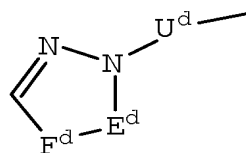
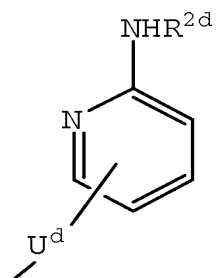
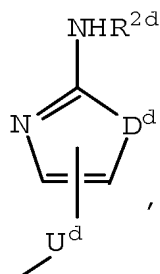
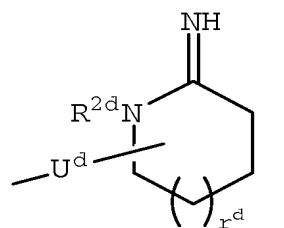
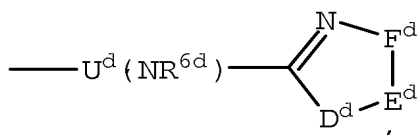
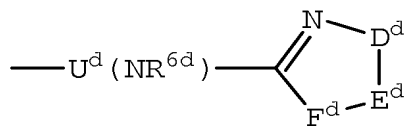
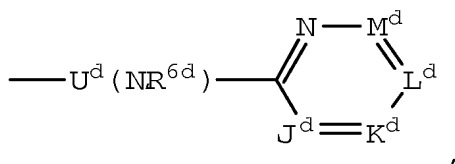
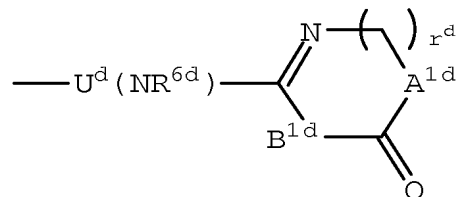
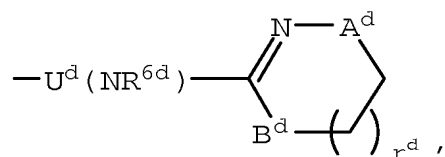
X^{4d} is CR^{11d}.

R^{1d} is R^{1de}, C₁-C₆ alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₃-C₆ alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₃-C₇ cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, C₄-C₁₁ cycloalkylalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d}, aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}, or aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}.

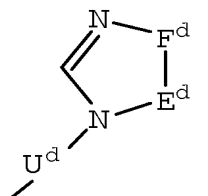
R^{1de} is:

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or



A^d and B^d are independently -CH₂-, -O-, -N(R^{2d})-, or -C(=O)-;

A^{1d} and B^{1d} are independently -CH₂- or -N(R^{3d})-;

D^d is -N(R^{2d})-, -O-, -S-, -C(=O)- or -SO₂-;

E^d, F^d is -C(R^{4d})=C(R^{5d})-, -N=C(R^{4d})-, -C(R^{4d})=N-, or -C(R^{4d})₂C(R^{5d})₂-;

J^d, K^d, L^d and M^d are independently -C(R^{4d})-, -C(R^{5d})- or -N-, provided that at least one of J^d, K^d, L^d and M^d is not -N-;

provided that when R^{1d} is R^{1de} then one of X^{1d} and X^{2d} is C- W^d- X^d- Y^d, and when R^{10d} is R^{1de} then X^{3d} is C- W^d- X^d- Y^d;

R^{2d} is H, C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonyl, (C₁-C₆ alkoxy)carbonyl; (C₁-C₆ alkyl)aminocarbonyl, C₃-C₆ alkenyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, heteroaryl(C₁-C₆ alkyl)carbonyl, heteroarylcarbonyl, aryl(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)carbonyl-, arylcarbonyl, C₁-C₆ alkylsulfonyl, arylsulfonyl, aryl(C₁-C₆ alkyl)sulfonyl, heteroarylsulfonyl, heteroaryl(C₁-C₆ alkyl)sulfonyl, aryloxy carbonyl, or aryl(C₁-C₆ alkoxy)carbonyl, wherein said aryl groups are substituted with 0-2 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and nitro;

R^{3d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, or heteroaryl(C₁-C₆ alkyl)-;

R^{4d} and R^{5d} are independently H, C₁-C₄ alkoxy, NR^{2d}R^{3d}, halogen, NO₂, CN, CF₃, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)carbonyl, (C₁-C₆ alkoxy)carbonyl, or arylcarbonyl, or

alternatively, when substituents on adjacent atoms, R^{4d} and R^{5d} can be taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or 5-7 membered heterocyclic aromatic or non-aromatic ring system, said carbocyclic or heterocyclic ring being optionally substituted with 0-2 groups selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, cyano, amino, CF₃, and NO₂;

U^d is:

_____-(CH₂)_n^d-,

-(CH₂)_n^d(CR^{7d}=CR^{8d})(CH₂)_m^d-,

$-(CH_2)_n^d(C\equiv C)(CH_2)_m^d-$,
 $-(CH_2)_n^dQ^d(CH_2)_m^d-$,
 $-(CH_2)_n^dO(CH_2)_m^d-$,
 $-(CH_2)_n^dN(R^{6d})(CH_2)_m^d-$,
 $-(CH_2)_n^dC(=O)(CH_2)_m^d-$,
 $-(CH_2)_n^d(C=O)N(R^{6d})(CH_2)_m^d-$,
 $-(CH_2)_n^dN(R^{6d})(C=O)(CH_2)_m^d-$, or
 $-(CH_2)_n^dS(O)_p^d(CH_2)_m^d-$;

wherein one or more of the methylene groups in U^d is optionally substituted with R^{7d} .

Q^d is selected from 1,2-cycloalkylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 2,3-pyridinylen, 3,4-pyridinylen, 2,4-pyridinylen, or 3,4-pyridazinylen;

R^{6d} is H, C_1 - C_4 alkyl, or benzyl;

R^{7d} and R^{8d} are independently H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_4 - C_{11} cycloalkylalkyl, aryl, aryl(C_1 - C_6 alkyl)-, or heteroaryl(C_0 - C_6 alkyl)-;

R^{10d} is H, R^{1de} , C_1 - C_4 alkoxy substituted with 0-1 R^{21d} , $N(R^{6d})_2$, halogen, NO_2 , CN, CF_3 , CO_2R^{17d} , $C(=O)R^{17d}$, $CONR^{17d}R^{20d}$, $-SO_2R^{17d}$, $-SO_2NR^{17d}R^{20d}$, C_1 - C_6 alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_6 alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_7 cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_4 - C_{11} cycloalkylalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d} , or aryl(C_1 - C_6 alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d} ;

R^{10de} is H, C_1 - C_4 alkoxy substituted with 0-1 R^{21d} , $N(R^{6d})_2$, halogen, NO_2 , CN, CF_3 , CO_2R^{17d} , $C(=O)R^{17d}$, $CONR^{17d}R^{20d}$, $-SO_2R^{17d}$, $-SO_2NR^{17d}R^{20d}$, C_1 - C_6 alkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_6 alkenyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_3 - C_7 cycloalkyl substituted with 0-1 R^{15d} or 0-1 R^{21d} , C_4 - C_{11} cycloalkylalkyl

substituted with 0-1 R^{15d} or 0-1 R^{21d}, aryl substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d}, or aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{15d} or 0-2 R^{11d} or 0-1 R^{21d};

R^{11d} is H, halogen, CF₃, CN, NO₂, hydroxy, NR^{2d}R^{3d}, C₁-C₄ alkyl substituted with 0-1 R^{21d}, C₁-C₄ alkoxy substituted with 0-1 R^{21d}, aryl substituted with 0-1 R^{21d}, aryl(C₁-C₆ alkyl)- substituted with 0-1 R^{21d}, (C₁-C₄ alkoxy)carbonyl substituted with 0-1 R^{21d}, (C₁-C₄ alkyl)carbonyl substituted with 0-1 R^{21d}, C₁-C₄ alkylsulfonyl substituted with 0-1 R^{21d}, or C₁-C₄ alkylaminosulfonyl substituted with 0-1 R^{21d};

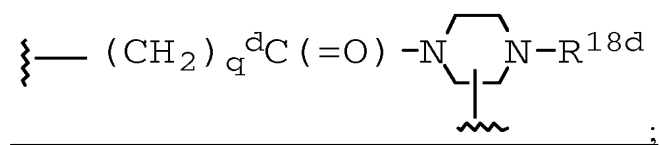
W^d is:

-(C(R^{12d})₂)_q^dC(=O)N(R^{13d})-, or

-C(=O)-N(R^{13d})-(C(R^{12d})₂)_q^d;

X^d is -C(R^{12d})(R^{14d})-C(R^{12d})(R^{15d})-; or

alternatively, W^d and X^d can be taken together to be



R^{12d} is H, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, (C₁-C₄ alkyl)carbonyl, aryl, or aryl(C₁-C₆ alkyl)-;

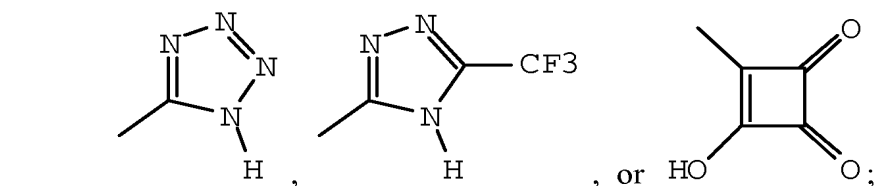
R^{13d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkylmethyl, or aryl(C₁-C₆ alkyl)-;

R^{14d} is:

H, C₁-C₆ alkylthio(C₁-C₆ alkyl)-, aryl(C₁-C₁₀ alkylthioalkyl)-, aryl(C₁-C₁₀ alkoxyalkyl)-, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxyalkyl, C₁-C₆ hydroxyalkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, heteroaryl(C₁-C₆ alkyl)-, aryl, heteroaryl, CO₂R^{17d}, C(=O)R^{17d}, or CONR^{17d}R^{20d}, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-1 R^{16d} or 0-2 R^{11d};

R^{15d} is H, R^{16d}, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxyalkyl, C₁-C₁₀ alkylaminoalkyl, di(C₁-C₁₀ alkyl)aminoalkyl, (C₁-C₁₀ alkyl)carbonyl, aryl(C₁-C₆ alkyl)carbonyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, heteroaryl(C₁-C₆ alkyl)-, aryl, heteroaryl, CO₂R^{17d}, C(=O)R^{17d}, CONR^{17d}R^{20d}, SO₂R^{17d}, or SO₂NR^{17d}R^{20d}, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-2 R^{11d}.

Y^d is -COR^{19d}, -SO₃H, -PO₃H, tetrazolyl, -CONHNHSO₂CF₃, -CONHSO₂R^{17d}, -CONHSO₂NHR^{17d}, -NHCOCF₃, -NHCONHSO₂R^{17d}, -NHSO₂R^{17d}, -OPO₃H₂, -OSO₃H, -PO₃H₂, -SO₃H, -SO₂NHCOR^{17d}, -SO₂NHCO₂R^{17d},



R^{16d} is:

-N(R^{20d})-C(=O)-O-R^{17d},
-N(R^{20d})-C(=O)-R^{17d},
-N(R^{20d})-C(=O)-NH-R^{17d},
-N(R^{20d})SO₂-R^{17d}, or
-N(R^{20d})SO₂-NR^{20d}R^{17d}.

R^{17d} is C₁-C₁₀ alkyl optionally substituted with a bond to the linking group, C₃-C₁₁ cycloalkyl optionally substituted with a bond to the linking group, aryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking group, (C₁-C₆ alkyl)aryl optionally substituted with a bond to the linking group, heteroaryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking group, (C₁-C₆ alkyl)heteroaryl optionally substituted with a bond to the linking group, biaryl(C₁-C₆ alkyl)- optionally substituted with a bond to the linking

group, heteroaryl optionally substituted with a bond to the linking group, aryl optionally substituted with a bond to the linking group, biaryl optionally substituted with a bond to the linking group, or a bond to the linking group, wherein said aryl, biaryl or heteroaryl groups are also optionally substituted with 0-3 substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, aryl, heteroaryl, halo, cyano, amino, CF₃, or NO₂;

R^{18d} is:

_____ -H,

_____ -C(=O)-O-R^{17d},

_____ -C(=O)-R^{17d},

_____ -C(=O)-NH-R^{17d},

_____ -SO₂-R^{17d}, or

_____ -SO₂-NR^{20d}R^{17d}.

R^{19d} is hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy, aryloxy, aryl(C₁-C₆ alkoxy)-, C₃-C₁₀ alkylcarbonyloxyalkyloxy, C₃-C₁₀ alkoxy carbonyloxyalkyloxy, C₂-C₁₀ alkoxy carbonylalkyloxy, C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonylalkyloxy, C₇-C₁₁ aryloxy carbonylalkyloxy, C₈-C₁₂ aryloxy carbonyloxyalkyloxy, C₈-C₁₂ arylcarbonyloxyalkyloxy, C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy, C₅-C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀-C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or

(R^{11d})(R^{12d})N-(C₁-C₁₀ alkoxy)-;

R^{20d} is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, or heteroaryl(C₁-C₆ alkyl)-;

R^{21d} is COOH or NR^{6d};

m^d is 0-4;

n^d is 0-4;

t^d is 0-4;

p^d is 0-2;

q^d is 0-2;

r^d is 0-2; and

d is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

with the following provisos:

(1) t^d, n^d, m^d and q^d are chosen such that the number of atoms connecting R^{1d} and Y^d is in the range of 10-14; and

(2) n^d and m^d are chosen such that the value of n^d plus m^d is greater than one unless U^d is



102. (Previously Presented) The composition of claim 101, wherein the receptor is $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

103. (Currently amended) The composition of claim 102, wherein the surfactant is a lipid or

a compound of the formula: $\text{A}^9\text{---E}^1\text{---A}^{10}$; wherein

A⁹ is selected from ~~the group: -OH and or~~ OR²⁷;

A¹⁰ is OR²⁷;

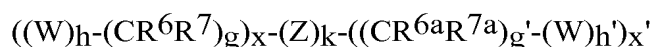
R²⁷ is C(=O)C₁₋₂₀ alkyl;

E¹ is C₁₋₁₀ alkylene substituted with 1-3 R²⁸;

R²⁸ is independently selected at each occurrence from ~~the group: R³⁰, -PO₃H-R³⁰, =O, -CO₂R²⁹, -C(=O)R²⁹, -C(=O)N(R²⁹)₂, -CH₂OR²⁹, -OR²⁹, -N(R²⁹)₂, C₁-C₅ alkyl, and or~~ C₂-C₄ alkenyl;

R²⁹ is independently selected at each occurrence from ~~the group:~~ R³⁰, H, C₁-C₆ alkyl, phenyl, benzyl, ~~and~~ or trifluoromethyl; and
R³⁰ is a bond to the linking group.

104. (Currently amended) The composition of claim 103, wherein the linking group has a formula:



wherein:

W is independently selected at each occurrence from ~~the group:~~ O, S, NH, NHC(=O), C(=O)NH, NR⁸C(=O), C(=O)NR⁸, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, SO₂NH, (OCH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂O)₂₀₋₂₀₀, (OCH₂CH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂CH₂O)₂₀₋₂₀₀, ~~and~~ or (aa)_{t'};

aa is independently at each occurrence an amino acid;

Z is selected from ~~the group:~~ aryl substituted with 0-3 R¹⁰, C₃-10 cycloalkyl substituted with 0-3 R¹⁰, ~~and~~ or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and~~ or O and substituted with 0-3 R¹⁰;

R⁶, R^{6a}, R⁷, R^{7a}, and R⁸ are independently selected at each occurrence from ~~the group:~~ H, =O, COOH, SO₃H, PO₃H, C₁-C₅ alkyl substituted with 0-3 R¹⁰, aryl substituted with 0-3 R¹⁰, benzyl substituted with 0-3 R¹⁰, ~~and~~ C₁-C₅ alkoxy substituted with 0-3 R¹⁰, NHC(=O)R¹¹, C(=O)NHR¹¹, NHC(=O)NHR¹¹, NHR¹¹, R¹¹, ~~and~~ or a bond to S_f the surfactant;

R¹⁰ is independently selected at each occurrence from ~~the group:~~ a bond to S_f the surfactant, COOR¹¹, C(=O)NHR¹¹, NHC(=O)R¹¹, OH, NHR¹¹, SO₃H, PO₃H, -OPO₃H₂, -OSO₃H, aryl substituted with 0-3 R¹¹, C₁-5 alkyl substituted with 0-1 R¹², C₁-5 alkoxy

substituted with 0-1 R¹², ~~and~~ or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and~~ or O and substituted with 0-3 R¹¹;

R¹¹ is independently selected at each occurrence from ~~the group~~: H, alkyl substituted with 0-1 R¹², aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, ~~and~~ or O and substituted with 0-1 R¹², C₃₋₁₀ cycloalkyl substituted with 0-1 R¹², ~~and~~ or a bond to ~~S_f~~ the surfactant;

R¹² is a bond to ~~S_f~~ the surfactant;

k is selected from 0, 1, ~~and~~ or 2;

h is selected from 0, 1, ~~and~~ or 2;

h' is selected from 0, 1, ~~and~~ or 2;

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ~~and~~ or 10;

x is selected from 0, 1, 2, 3, 4, ~~and~~ or 5; and

x' is selected from 0, 1, 2, 3, 4, ~~and~~ or 5.

105. (Previously Presented) The composition of claim 104, further comprising: 1,2-dipalmitoyl-sn-glycero-3-phosphatidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine.

106. (Previously Presented) The composition of claim 105, wherein the echogenic gas is a C₂₋₅ perfluorocarbon.

107. (Canceled)

108. (Previously Presented) A therapeutic composition, comprising:
the composition of claim 76 and a parenterally acceptable carrier.

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**PATENT
REPLY FILED UNDER EXPEDITED
PROCEDURE PURSUANT TO
37 CFR § 1.116**

109. (Previously Presented) A diagnostic composition, comprising:
the composition of claim 76 and a parenterally acceptable carrier.
110. (Previously Presented) An ultrasound contrast agent composition, comprising:
composition of claim 101 and a parenterally acceptable carrier.